Role of non-nicotine tobacco constituents in the abuse liability of E-cigarettes

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Background

- Electronic cigarettes (E-cigarettes) are increasing in popularity in the United States[1] and may be an effective and safe method to help people quit smoking conventional cigarettes[2,3]
- However, E-cigarettes may be harmful to one's physical health[4]
- E-cigarettes contain nicotine, the main addictive component of tobacco[5], meaning E-cigarettes have abuse liability
- Nicotine is considered to be addictive because of its primary reinforcing effects and its ability to enhance the reinforcing effects of other stimuli (reinforcement enhancement)[6]
- However, too much nicotine leads to aversive effects, limiting the amount of drug intake[6]
- The abuse liability of conventional cigarettes is not only due to the presence of nicotine, but also to the presence of other constituents, like minor alkaloids[6]
- The solution used in E-cigarettes also contains other constituents, including minor alkaloids[7,8], which may influence this product's abuse liability as well
- Not much research has been done on the components of E-cigarettes, but it is essential to understand their effects so that the use of E-cigarettes can be better regulated

Goal of Study

- The goal of the study was to test the hypothesis:
  - Since non-nicotine constituents can enhance nicotine's addictive effects in other models[6], E-cigarette solution will have greater reinforcement enhancement at low to moderate doses of nicotine and reduced aversive effects at high doses of nicotine when compared to the same dose of nicotine alone, therefore having an increased abuse liability

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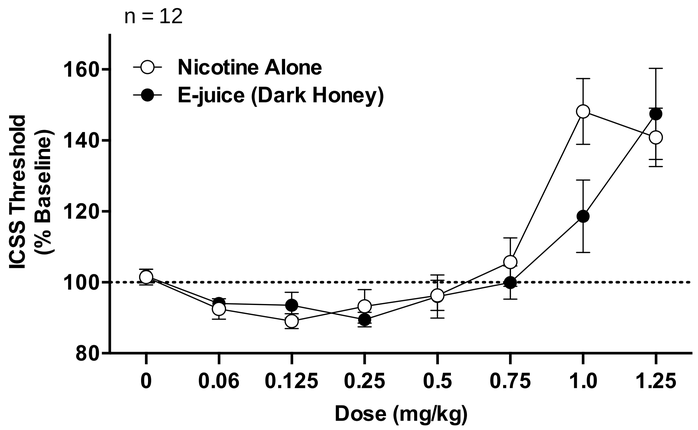
Methods

- A rat model was used because it provides an accurate representation of the human reaction to nicotine, it allows for control of variables, and the use of human subjects is avoided[9]
- The reinforcement enhancement and aversive effects of nicotine were modeled using intracranial self-stimulation (ICSS)
- Using the ICSS model, rats are allowed to respond for rewarding electrical brain stimulation[10], and in trials where the stimulation gradually decreases in intensity, there becomes a point where the stimulation is no longer rewarding enough to maintain the rat's response, called the ICSS threshold
- The rats used in the experiment were male Holtzman Sprague-Dawley rats housed in a reversed 12 hour light/dark cycle with ICSS electrodes implanted in the lateral hypothalamus using well-established procedures[6]
- The rats were trained on the ICSS procedure according to Vlachou[10]
- Once the rats had stable ICSS thresholds, twice per week they were injected with solutions of nicotine in a saline solution or Dark Honey E-cigarette solution containing nicotine concentrations of 0, 0.06, 0.125, 0.25, 0.50, 0.75, 1.0, or 1.25 mg/kg in a counterbalanced order
- The ICSS thresholds of the rats were tested 10 minutes after the injection, which allowed time for the drug to distribute to the brain
- Rats were tested for their ICSS thresholds on the days that they were not given drug injections to ensure that their thresholds returned to baseline between injections



Results

- The experiment is not yet complete since data from more rats is needed to find significant differences
- The preliminary data, shown in Figure 1, indicates that there is no difference between nicotine alone and the E-cigarette solution at low to moderate doses of nicotine
- The decrease in the ICSS threshold at low to moderate doses means that a lower intensity of stimulation will maintain the rat's behavior, reflecting the reinforcement enhancement effects of nicotine
- The E-cigarette solution appears to show a lower ICSS threshold than nicotine alone at a dose of 1.0 mg/kg (high dose)
- At higher doses of nicotine, the increased ICSS threshold means that it takes higher levels of stimulation for the rat to maintain its previous behavior, reflecting the aversive effects of nicotine

Conclusions

- Again, since there were not enough rats in the experiment, significant conclusions cannot yet be made
- The preliminary data indicates that the non-nicotine components of the E-cigarette solution do not play a role in the reinforcement enhancement properties of the product since the difference from baseline is similar to that of nicotine alone
- This may indicate that the non-nicotine constituents of E-cigarettes do not influence the product's abuse liability
- However, the E-cigarette solution's lower ICSS threshold at a dose of 1.0 mg/kg may indicate that other constituents in the solution have a role in limiting the aversive effects, which may mean that more of the drug could be taken before the aversive effects occur, increasing its abuse liability

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Figure 1. Mean ICSS thresholds compared to baseline of rats given injections of nicotine alone or Dark Honey E-cigarette solution at doses of varying nicotine concentrations. The ICSS thresholds were found of 12 rats given either nicotine alone or E-cigarette solution at varying doses of nicotine. Each dot represents the mean ICSS threshold as a percentage of the baseline at each dose, and the error bars represent the standard error of the mean.